



CRITICAL REVIEW

# Bacterial co-infections with SARS-CoV-2

Rasoul Mirzaei<sup>1,2</sup>  | Pedram Goodarzi<sup>3</sup> | Muhammad Asadi<sup>4</sup> | Ayda Soltani<sup>5</sup> | Hussain ali abraham Aljanabi<sup>4,6</sup> | Ali Salimi Jeda<sup>7</sup> | Shirin Dashtbin<sup>8</sup> | Saba Jalalifar<sup>8</sup> | Rokhsareh Mohammadzadeh<sup>8</sup> | Ali Teimoori<sup>9</sup> | Kamran Tari<sup>2,10</sup> | Mehdi Salari<sup>2,10</sup> | Sima Ghiasvand<sup>1</sup> | Sima Kazemi<sup>1</sup> | Rasoul Yousefimeashouf<sup>1</sup> | Hossein Keyvani<sup>7</sup> | Sajad Karampoor<sup>7</sup> 

<sup>1</sup>Department of Microbiology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>2</sup>Student Research Committee, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>3</sup>Faculty of Pharmacy, Iran University of Medical Sciences, Tehran, Iran

<sup>4</sup>Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran

<sup>5</sup>School of Basic Sciences, Ale-Taha Institute of Higher Education, Tehran, Iran

<sup>6</sup>Alnahrain University College of Medicine, Iraq

<sup>7</sup>Department of Virology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

<sup>8</sup>Department of Microbiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

<sup>9</sup>Department of Virology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>10</sup>Department of Environmental Health Engineering, Hamadan University of Medical Sciences, Hamadan, Iran

## Correspondence

Sajad Karampoor, Ph.D. of Medical Virology, Department of virology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

Email: sajadkarampoor1987@gmail.com

Rasoul Mirzaei, Ph.D. of Medical Microbiology, Department of Medical Microbiology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran.

Email: rasul.micro92@gmail.com

Hossein Keyvani, Department of Virology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

Email: H.keyvani@iums.ac.ir

## Abstract

The pandemic coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has affected millions of people worldwide. To date, there are no proven effective therapies for this virus. Efforts made to develop antiviral strategies for the treatment of COVID-19 are underway. Respiratory viral infections, such as influenza, predispose patients to co-infections and these lead to increased disease severity and mortality. Numerous types of antibiotics such as azithromycin have been employed for the prevention and treatment of bacterial co-infection and secondary bacterial infections in patients with a viral respiratory infection (e.g., SARS-CoV-2). Although antibiotics do not directly affect SARS-CoV-2, viral respiratory infections often result in bacterial pneumonia. It is possible that some patients die from bacterial co-infection rather than virus itself. To date, a considerable number of bacterial strains have been resistant to various antibiotics such as

**Abbreviations:** AMPs, antimicrobial peptides; CCL2, C-C Motif Chemokine Ligand 2; COVID-19, coronavirus disease 2019; HCoV, human coronavirus; HCoV-NL63, Human coronavirus NL63; ICAM-1, intercellular adhesion molecule 1; IFNs, interferons; IL, interleukin; IP-10, interferon- $\gamma$ -inducible protein-10; IRF-3, interferon regulatory factor 3; MAVS, mitochondrial antiviral-signaling; MCP-1, monocyte chemoattractant protein-1; MDA5, RIG-1/melanoma differentiation-associated gene 5; MERS, Middle East Respiratory Syndrome-related coronavirus; NADPH, nicotinamide adenine dinucleotide phosphate; NTHI, non-typeable *H. influenzae*; PERK, PKR-like endoplasmic reticulum kinase; PKR, protein kinase R; REG3B, Regenerating Islet Derived Protein 3 Beta; RIG-I, retinoic acid-inducible gene 1; SARS, severe acute respiratory syndrome; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; STAT1, signal transducer and activator of transcription 1; TANK, TRAF Family Member Associated NFKB Activator; TB, tuberculosis; TGF- $\beta$ , transforming growth factor-beta; TLR-3, Toll-like receptor 3; TRAF3, TNF Receptor Associated Factor 3; T4P, Type 4 pilus; WGMs, whole-genome metagenomics.

azithromycin, and the overuse could render those or other antibiotics even less effective. Therefore, bacterial co-infection and secondary bacterial infection are considered critical risk factors for the severity and mortality rates of COVID-19. Also, the antibiotic-resistant as a result of overusing must be considered. In this review, we will summarize the bacterial co-infection and secondary bacterial infection in some featured respiratory viral infections, especially COVID-19.

#### KEYWORDS

antibiotic, bacterial co-infection, COVID-19, SARS-CoV-2, viral infection

## 1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first identified in December 2019 in Wuhan, China, and is currently circulating throughout the world.<sup>1</sup> By July 5, 2020, more than 11,125,245 million cases have been diagnosed in 216 countries, and more than 528,204 deaths have been reported.<sup>2</sup> The ongoing COVID-19 pandemic highlights the critical need for rapid development of vaccines and antiviral treatments to reduce the number of hospitalizations and deaths caused by this new dangerous coronavirus.<sup>3</sup> Co-infections and superinfections are common in respiratory viral infections.<sup>4,5</sup> According to the laboratory, clinical, and epidemiological studies, secondary or bacterial co-infections with other viruses can significantly increase the mortality rate in patients infected with viral infections.<sup>6,7</sup> It has previously documented that the mortality rate of viral infections can be influenced by different factors, such as bacterial co-infection.<sup>8–10</sup> For instance, influenza-related bacterial infections contribute to severe illness and mortality during the epidemic and seasonal influenza outbreaks.<sup>11</sup> Some influenza-related bacterial species include *Streptococcus pyogenes*, *Neisseria meningitidis*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*.<sup>11–18</sup> The mechanisms of severe complications caused by influenza-bacterial co-infections mainly include a lack of effective immune response as well as pathogenic synergy.<sup>5</sup> Although multiple microbial agents can cause acute lower respiratory tract infections, in most cases, the disease is caused by viruses and bacteria at the same time.<sup>19</sup> Secondary and bacterial co-infections with pandemics and viral epidemics have irreversible consequences, especially in high-risk groups, including those with immunodeficiency or immunosuppression.<sup>20</sup>

Emerging evidence suggests that the number of patients with COVID-19 diagnosed with bacterial

co-infections during hospitalization periods is increasingly raised.<sup>21–23</sup> The source and specific nature of these infections are yet to be fully explored, but there is some evidence suggesting that multidrug-resistant bacteria are among the pathogens that are thought to be responsible for the development of these infections.<sup>21–23</sup> Patients vulnerable to viral lung infections, such as influenza, severe acute respiratory syndrome (SARS), and COVID-19 are the greatest risk to be co-infected with superbugs.<sup>21–25</sup> For example, the 2009 H1N1 influenza pandemic caused approximately 300,000 deaths around the world in which 30–55% of cases die of bacterial pneumonia.<sup>26,27</sup> It is now known that viral infections can weaken the host immunity, paving the way for the development of viral-bacterial co-infection.<sup>28,29</sup> The new coronavirus, COVID-19, is another example of this fact as most of the hospitalized patients with COVID-19 acquired a secondary bacterial infection.<sup>30–32</sup> In some severe form of SARS-CoV-2, patients exhibited increased levels of infection-related biomarkers and inflammatory cytokines, suggesting potential bacterial co-infection as a result of the dysregulated immune system.<sup>33</sup> Besides, the emergence of antibiotic resistance could be an additional burden for the health care system as co-infection with coronavirus and pneumonia stretches health care units beyond their capabilities and resources. Understanding the mechanism underlying the synergy between Covid-19 and bacteria paves the way for the discovery of novel therapeutic agents to prevent the mortality rate in patients co-infected with COVID-19 and bacteria. In the current situation, appropriate and systematic analysis of COVID-19 patients diagnosed with bacterial co-infection should be implemented to choose proper antibiotics to increase the survival of patients and limit the spread of drug-resistant bacteria. The use of rapid diagnostic tools and methods promoting the prescription of effective narrow-spectrum antibiotics should be taken into account. In this review, we will summarize the current data available for bacterial infections in patients with COVID-19.

## 1.1 | Bacterial co-infection with viral respiratory infections

Viral pneumonia and lower respiratory tract infections are well characterized in adult patients, including those diagnosed with severe forms of viral infection.<sup>34</sup> Most viral lower respiratory tract infections seem to be acquired in the community and considered a leading cause of infection in patients who undergo mechanical ventilation.<sup>34</sup> The most common cases diagnosed with bacterial co-infection with viral infections are seen in those infected with influenza virus.<sup>27</sup> The oldest report of bacterial infections that occurred simultaneously or shortly after influenza is related to the 1918 Influenza pandemic, in which most deaths occurred as a result of co-infection with infectious bacteria.<sup>35</sup> Also, the H1N1 Influenza pandemic in 2009 was complicated by bacterial pneumonia in 4–33% of hospitalized patients.<sup>36–38</sup> Bacterial-viral co-infection is not restricted to influenza and also caused by other respiratory viruses, such as parainfluenza virus, respiratory syncytial virus, adenovirus, rhinovirus, and human metapneumovirus.<sup>34,39,40</sup> Despite the discovery of antibiotics and viral vaccines in 1918–1957, the mortality rate, resulting from secondary bacterial pneumonia remained a major problem. The mortality rate seems to be still growing mostly because of the rapid rate of aging in the human population.<sup>41,42</sup>

Although viruses are commonly responsible for the development of acute upper and lower respiratory infections, in most cases patients may be infected by both bacterial and viral pathogens; however, the clinical manifestations at the early stages of the disease would not be nosologically distinguishable for physicians to differentially diagnose viral from a bacterial infection.<sup>43</sup> Recently, a group of respiratory emerging viruses has been identified, such as human coronavirus (HCoV), NL63, human bocavirus, influenza viruses' type H1N1 and H5N1, SARS, Middle East Respiratory Syndrome-related coronavirus (MERS), and Covid-19.<sup>44–48</sup> In children, atypical bacterial pathogens, such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* include the majority of infectious agents that cause mild, moderate, or even severe forms of acute respiratory infections.<sup>49,50</sup> Bacterial co-infections with respiratory viral pathogens are very common, often through synergistic interaction among viruses such as influenza virus, and bacterial pathogens and the host immune system of the human being; nevertheless, the interaction between viruses and unusual bacteria is not yet fully understood.<sup>50,51</sup> These secondary infections predominantly involve a specific group of bacterial pathogens, such as *S. aureus*, *S. pneumoniae*, *S. pyogenes*, and *H. influenzae*.<sup>11–18</sup> A complete list of bacterial co-infections with viral pathogens is depicted in Table 1.

## 1.2 | Viral predisposition to bacterial co-infection in the respiratory tract

Commonly, viral infection can destroy histologically and functionally the respiratory tract of individuals upon viral spread.<sup>42</sup> Depending on the type of the virus, the histopathological outcomes could be relatively different from mild types to severe ones. These detrimental changes include altered mucus secretion, cell death, hyperplasia, decreased mucosal clearance, reduced oxygen exchange, and impaired surfactant secretion.<sup>42,77</sup> Each of these effects is caused by various molecular mechanisms, depending on the virus, bacterial species, as well as the degree of the host immune reaction to either a bacterium or virus.<sup>42</sup> It has been noted that viral infections promote bacterial colonization of the airway through a variety of mechanisms.<sup>42</sup> Peltola and colleagues found that influenza viruses can enhance the colonization of the nasopharynx by *S. pneumoniae* bacterium, however, only particular subtypes were found to mediate the development of bacterial otitis media and sinusitis.<sup>78</sup> These data explain why the rate of bacterial infection is high in influenza seasons.<sup>42</sup> The neuraminidase enzyme of the influenza virus has been found to be presented on the host cell receptors, and they are employed for the adherence of bacteria due to its sialidase ability that changes the carbohydrate moieties on the host epithelial cells.<sup>77,79</sup> This enzyme is also capable of increasing the possibility of bacterial adherence to the host cells through the stimulation of transforming growth factor-beta (TGF- $\beta$ ) which triggers the up-regulation of integrins and fibronectin. Integrins and fibronectin have been shown to act as receptors for bacteria.<sup>80</sup> Besides, interferons (IFNs) induction by influenza virus can cause reduced C-C Motif Chemokine Ligand 2 (CCL2) expression resulting in failed macrophages recruitment that necessary for clearance of pneumococcal cells thereby enhance the colonization of *S. pneumoniae* in vivo.<sup>81</sup> Also, it has been found that the influenza virus predisposes the host to develop pneumonia caused by *S. aureus* where viral and bacterial loads are increased during co-infection.<sup>52</sup> It has been hypothesized that viral load is increased following bacterial co-infection because of increased shedding rate of the virus from infected host cells; however, bacterial loads would be elevated as a result of impaired function of alveolar macrophages.<sup>82</sup>

Additionally, other upper respiratory tract viruses increase the adherence ability of bacterial pathogens to primary and immortalized epithelial cells with particular differences. Such differences are determined by the types of epithelial cells and their response to parainfluenza virus-3, respiratory syncytial virus, and/or influenza virus.<sup>83</sup> Novotny et al<sup>84</sup> showed that adenovirus and respiratory

**TABLE 1** Common respiratory viral-bacterial coinfections and their associated clinical infections in human

Viral infection	Bacterial coinfection	Clinical infection	References
Influenza	<i>Staphylococcus aureus</i> , MRSA	Community-acquired pneumonia,	18,52–57
	<i>Streptococcus pneumoniae</i>	Pneumococcal pneumonia, sepsis, meningitis, otitis media	58
	<i>Streptococcus pyogenes</i> (group A streptococci)	Sepsis, pleural empyema	15
	<i>Haemophilus influenzae</i>	Pneumonia	59
	<i>Moraxella catarrhalis</i>	Pneumonia and bacteremia	60,61
	<i>Neisseria meningitidis</i>	Meningococemia	62,63
	<i>Chlamydophila pneumoniae</i>	Pneumonia	64
	<i>Mycoplasma pneumoniae</i>	Pneumonia	64
	<i>Legionella pneumophila</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i> , <i>Burkholderia cepacia</i> , <i>Enterobacter aerogenes</i>	Pneumonia	57
Metapneumovirus	<i>Haemophilus influenzae</i> , enterococcus spp, <i>N. meningitidis</i> group B, <i>Brucella</i> spp, <i>Streptococcus pyogenes</i> , <i>Streptococcus pneumoniae</i>	Acute otitis media, pneumonia	65
Respiratory syncytial virus	<i>Pseudomonas aeruginosa</i>	Respiratory infections in cystic fibrosis patients	66,67
Adenovirus	Non-typeable <i>Haemophilus influenzae</i> , <i>Chlamydia trachomatis</i>	Pneumonia or acute otitis media	68
Parainfluenza	<i>Streptococcus pneumoniae</i> , <i>Streptococcus agalactiae</i> , <i>Haemophilus influenzae</i>	Acute otitis media, pneumonia	69,70
Rhinovirus	<i>Streptococcus pneumoniae</i> , <i>Mycoplasma</i>	Pneumonia	50
	<i>Staphylococcus aureus</i>	Respiratory complications	71
SARS	<i>Chlamydophila pneumoniae</i> , <i>Mycoplasma pneumoniae</i>	Pneumonia	72
	MRSA	Pneumonia	73,74
MERS	<i>Mycobacterium tuberculosis</i>	Immune suppression and augment the infection of each other	75
	<i>Mycoplasma</i> spp.	Not reported	76
	<i>Legionella</i>		
	<i>Chlamydia</i> spp.		

Abbreviations: MERS, Middle East respiratory syndrome; MRSA, methicillin-resistant *Staphylococcus aureus*; SARS, severe acute respiratory syndrome.

syncytial virus stimulated the expression of intercellular adhesion molecule 1 (ICAM-1) by primary respiratory tract epithelial cells. ICAM1 acts as a receptor for Type 4 pilus (T4P) of non-typeable *H. influenzae* (NTHI), thus promoting the binding of this pathogen to cells expressing this molecule. Also, respiratory syncytial virus infection increases the binding ability of *P. aeruginosa* to normal epithelial cells, as well as cells affected by cystic fibrosis. Such phenomena have been frequently employed by other

bacteria to increase their virulence to infect the cells.<sup>66</sup> Studies have indicated that, following the infection with the respiratory syncytial virus, the rate of the binding of *S. pneumoniae* serotypes epithelial cells is increased by 2–10 folds.<sup>85</sup> Similarly, the antibody titers against *S. pneumoniae* are elevated in the nasopharynx when the cells co-infected with the respiratory syncytial virus, rhinovirus, and community-acquired pneumonia.<sup>86</sup> The higher degree of colonization of nasopharynx with *S. pneumoniae*

is also found when the individuals are co-infected with viral upper respiratory tract infection or human immunodeficiency virus infection.<sup>87</sup>

Bacterial and viral co-infection can alter some properties of the host mucosal immunity, leading to the failure in controlling the replication of bacteria in this site.<sup>88,89</sup> Some key findings are discussed here, including the influence of viral infection on phagocytic activity. The reduction of alveolar macrophages by the influenza virus facilitates bacterial co-infection.<sup>88,90</sup> Several lines of evidence demonstrated that 90% of resident alveolar macrophages were lost in the early weeks after influenza infection through tracking dye-labeled alveolar macrophages,<sup>42</sup> whereas 95% of the initial bacterial inoculum was eliminated during 3 hr by alveolar macrophages in non-influenza inoculated hosts. Notably, in those cells co-infected with influenza virus about 50% of the bacterial inoculum remained recoverable.<sup>42</sup> Also, it has been suggested that phagocyte activity, along with the cell proliferation could be influenced by viral infection. The infection of alveolar macrophages with influenza causes a marked decrease in the level of cytokines and chemokines, leading to decreased rates of recruitment and stimulation of neutrophils.<sup>88</sup> It may also suppress the phagocytic bacterial clearance mediated to nicotinamide adenine dinucleotide phosphate (NADPH), thereby increasing the susceptibility to secondary bacterial infection.<sup>91</sup> As mentioned earlier, the dysregulation of pro-inflammatory cytokine-induced by viral infection has been shown to play an essential role in the susceptibility of the cells to secondary bacterial infection. It is now known that type 1 IFNs have antiviral and immune-stimulatory properties and could have detrimental effects on human cells when their expression is inappropriate and excessive. It has been reported that IFNs play a fundamental role in the production of anti-inflammatory cytokines, such as interleukin (IL)-10 and IL-6, as well as the inhibition of proinflammatory cytokines, linking the innate immunity to adaptive immune responses, such as IL-17 and IL-23. They also decrease the activity of macrophages, dendritic cells, natural killer cells, along with the number of CD4- and CD8-positive T cells, leading to the impaired eradication of bacterial co-infection.<sup>79,92–94</sup>

Also, there are a number of mechanisms that are independent of the phagocytosis process by which viral host infection can predispose the human body to secondary bacterial co-infection. The production of antimicrobial peptides (AMPs), such as lipocalin-2, cathelicidin, Regenerating Islet Derived Protein 3 Beta (REG3B), calprotectin, may be dysregulated by upper respiratory tract viruses.<sup>94</sup> The respiratory syncytial virus infection is able to diminish the expression of human  $\beta$ -defensin-3 orthologue named chinchilla beta-defensin 1 when used in vivo. Of note, con-infection with the respiratory

syncytial virus is capable of stimulating the viral load of *Nontypeable Haemophilus influenzae* (NTHi) in the nasopharynx by 10–100 folds.<sup>95</sup> The intranasal delivery of anti-chinchilla beta-defensin 1, human  $\beta$ -defensin 3, or the recombinant form of chinchilla beta-defensin 1 showed that the disruption of the availability of even a single innate immune effector could have a great impact on bacterial load since the viral infection has a critical in the loading of *H. influenzae* within the host airway.<sup>95</sup> Some mechanisms by which viral respiratory infections may predispose patients to bacterial infections to include failure immune response, viral-induced changes in epithelial cells, and the increased bacterial colonization<sup>34</sup> and summarize of the potential mechanisms responsible for bacterial coinfection with viral respiratory infections is depicted in Table 2.

### 1.3 | Coronaviruses influence on host immune system

The human immune reaction to SARS-CoV-2 infection is a two-step reaction that during the non-severe infection phase, a particular adaptive immune reaction is necessary to viral eradicate and prevent the disease from progressing to a severe phase.<sup>127,128</sup> Hence, approaches to increase immune reactions such as using anti-serum and Pegylated IFN $\alpha$  are crucial at this phase.<sup>127,128</sup> To provide a protective immune reaction in the early phase, the host must be in a good general health condition and have a genetic background to be able to exhibit an acceptable antiviral reaction. Genetic diversity is well known to involve in particular changes in the host immune response to various microbial pathogens.

There is few information about the initial events in the process of virus elimination and inflammatory reactions during SARS-CoV infection. However, the innate immune reactions is mediated to the adaptive immunity development and disease severity in SARS-CoV.<sup>129</sup> Of note, SARS-CoV evolved escape mechanisms to avoid IFN responses in infected host cells. Besides, inflammatory reactions are regulated by inflammatory cytokines and chemokines such as IL-6, interferon- $\gamma$ -inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1) as well as the penetration of inflammatory cells such as macrophages into infected host tissues.<sup>129</sup> The suppression of antiviral type I interferons is one of the marked characteristics of SARS-CoV infection as well as other group II coronaviruses including mouse hepatitis virus.<sup>130</sup> It has been shown that the formation of type I interferons is impaired in host cells infected with SARS-CoV, but pretreatment of cells with IFN suppresses the growth of SARS-CoV.<sup>131,132</sup> This shows that these viruses



**TABLE 2** Summary of the potential mechanisms responsible for the bacterial coinfection with viral respiratory infections

Mechanism	Description	References
Elevation in bacterial adherence due to viral infection	Virus can modulate surface membrane receptors, thereby enhancing bacterial adhesion	16,96–98
Cell destruction by viral enzymes	Viral enzymes destroy mucosal glycoproteins, mainly those inhibiting bacterial attachment	98,99
Reduction of mucociliary clearance	Virus can reduce mucociliary clearance leading to the decreased production of bactericidal materials	100
Reduction in chemotaxis	Virus can decrease the chemotactic factors, leading to the reduced cell response to attacking organisms	101
Direct effect on phagocytic and induction of post phagocytic alveolar macrophage functions	Virus hinders or modifies a number of immune functions, such as phagosome-lysosome fusion and intracellular killing	102,103
Induction of immature phagocytes	Virus can disrupt macrophages and probably replace them with immature phagocytes	98,104,105
Reduction of surfactant levels	Virus impairs the function of alveolar type-2 pneumocyte	98,106,107
Induction of dysbiosis in lower respiratory tract microbiome	Microbiome dysbiosis can affect the immune response against respiratory viral infection	108
Dysregulation of the innate and adaptive immune responses	Virus decreases the number of alveolar macrophages through the development of apoptosis	42,88,90,91
Modulation of apoptosis and inflammation	Autophagy and apoptosis facilitates secondary bacterial pneumonia after viral infection	109
Reduction of antibacterial immune function at the respiratory epithelium	Respiratory viral infection leads to the predisposition to secondary bacterial infection via the deviation of the respiratory tract immune status	110–115
Dysregulation of nutritional immunity	Some viruses can subvert nutritional protection to promote bacterial infection	116–118
Immunosuppression	Immunosuppression is induced by several viruses such as HIV	119–121
Synergism during viral/bacterial co-infections	Both viruses and bacteria play a role in the immunopathogenicity of co-infection	8,122,123
Release of planktonic bacteria from biofilms	Viruses can manipulate many factors such as chemokines and hydrogen peroxide, thereby leading to the disruption of biofilm structure	42,124–126

Abbreviation: HIV, human immunodeficiency viruses.

have developed mechanisms to overcome IFN responses in infected cells. Type I interferons are rarely found in acute SARS patients, and SARS-CoV is sensitive to

Pegylated IFN- $\alpha$ , as shown in in vivo murine models.<sup>133</sup> Studies indicated that type I interferon suppression in SARS-CoV-infected hosts is mediated by the inactivation

of the IRF-3 (interferon regulatory factor 3) protein, a transcriptional factor that controls the transcription of interferons.<sup>132</sup> Also, other SARS-CoV accessory proteins act as powerful interferon antagonists through various strategies.<sup>129</sup> For instance, N proteins inhibit the expression of interferons, whereas open-reading frame 3b and 6 proteins oppress the signaling pathway and expression of interferons.<sup>129</sup> Also, open-reading frame 6 proteins can halt the translocation of signal transducer and activator of transcription 1 (STAT1). The open-reading frame 3b protein is a shuttling protein, impeding the stimulation of type I interferon, which is triggered by retinoic acid-inducible gene 1 (RIG-I) and mitochondrial antiviral-signaling (MAVS) protein.<sup>134</sup> Additionally, M proteins suppress the production of type I interferon by inhibiting the generation of the TNF Receptor Associated Factor 3 (TRAF3)-TRAF Family Member Associated NFKB Activator (TANK) – TANK binding kinase 1 (TBK1)/IkB kinase  $\epsilon$  (IKK $\epsilon$ ) complex.<sup>134</sup> Besides, SARS-CoV NSP1 proteins are able to halt the expression of IFN- $\beta$  in host cells by promoting the degradation of the host mRNA and the suppression of the translation process.<sup>135</sup> A polyprotein complex of SARS-CoV named papain-like protease is able to inhibit the phosphorylation and nuclear translocation of IRF-3, resulting in disrupting the activation of type I IFN response via either Toll-like receptor 3 (TLR-3) or RIG-1/melanoma differentiation-associated gene 5 (MDA5) complex.<sup>136</sup> Also, infected cells with SARS-CoV can stimulate the expression of protein kinase R (PKR) and PKR-like endoplasmic reticulum kinase (PERK).<sup>137</sup>

#### 1.4 | Bacterial co-infection with coronaviruses and COVID-19

Although numerous studies performed on viral and bacterial co-infections, little information exists about human coronaviruses. In addition to seasonal influenza, it has been reported corona pathogens of pneumonia include coronavirus 229E, NL63, OC43, SARS, MERS, and SARS-CoV-2. These viruses can cause co-infection in the setting of community-acquired bacterial pneumonia.<sup>138–141</sup> Human coronavirus NL63 (HCoV-NL63) has been recently discovered as a human respiratory pathogen with a high worldwide prevalence.<sup>142,143</sup> Arguably, HCoV-NL63 is among the most clinically significant human coronaviruses and associated with upper and lower respiratory tract infections, frequently occurring in the winter and presenting more severe symptoms in children, the elderly, and immunocompromised patients.<sup>142–144</sup> In a study conducted by Golda et al.,<sup>143</sup> they evaluated the impact of HCoV-NL63 on bacterial adherence causing respiratory tract diseases. HCoV-NL63

infection has been shown to enhance the adherence of *S. pneumoniae* to cells infected with the virus.<sup>143</sup> In one study, Zahariadis et al.<sup>72</sup> showed the coinfection of SARS patients with other pulmonary pathogens. They found that 30 and 9% of cases with SARS were co-infected with *C. pneumoniae* or *M. pneumoniae*, respectively. Additionally, Alfaraj et al.<sup>75</sup> reported the coinfection of MERS-CoV with tuberculosis (TB) in two cases. In a study carried out by Wang et al.,<sup>145</sup> they reported seven cases of SARS-related deaths who developed a secondary bacterial infection.

The COVID-19 pandemic caused a large number of immunocompromised individuals to be hospitalized and some reports indicated that some COVID-19 patients were diagnosed with secondary infections.<sup>30–32</sup> The specific source and nature of these infections have not yet been fully investigated; however, there is evidence indicating that multidrug-resistant bacteria are among those microbes responsible for the development of these secondary infections. In one study, five cases (5.1%) with bacterial co-infections including *Acinetobacter baumannii* and *Klebsiella pneumoniae* were found among 99 patients,<sup>146</sup> while in another study, four cases (9.8%) with secondary bacterial infections were reported among 41 patients.<sup>147</sup> In a study performed by Zhang et al.,<sup>148</sup> 221 patients with SARS-CoV-2 pneumonia were admitted to Zhongnan Hospital, Wuhan, China. Among them, 25.8% (57/221) patients were afflicted with co-infections, and among these patients with co-infections, 29.8% (17/57) were co-infected with bacteria. In a study conducted by Blasco et al.,<sup>149</sup> they detected one patient who was positive for *M. pneumoniae* coinfection among patients with COVID-19 pneumonia. Also, Claire et al.<sup>150</sup> reported a fatal case of necrotizing pneumonia induced by Panton-Valentine leukocidin-secreting *S. aureus* in a patient who was affected by COVID-19.

Some patients infected with SARS-CoV-2 showed the increased levels of biomarkers and inflammatory cytokines related to co-infection by bacteria, caused by dysregulation in the immune system.<sup>33</sup> The management of the severe form of SARS-CoV-2 is similar to most viral pneumonia-causing respiratory failure. In a study carried out by Bordi et al.,<sup>151</sup> they detected *M. pneumoniae* in five patients (4.0%), while only one patient was infected with *L. pneumophila* and *S. pneumoniae* (0.8%), and mixed infections were also observed in a small number of cases. They found the importance of using a broad-spectrum molecular diagnostic panel for rapid detection of the most common respiratory pathogens to improve evaluation and clinical management of patients with a respiratory syndrome consistent with COVID-19.<sup>151</sup> A list of bacterial co-infection with COVID-19 is depicted in Table 3.

One reason for this bacterial co-infection is due to many hospital-associated bacteria being adapted to develop

**TABLE 3** List of bacterial co-infection with COVID-19

Bacterium	Infection	References
<i>Staphylococcus aureus</i>	Necrotizing pneumonia	152
<i>Mycoplasma pneumoniae</i>	Exacerbate clinical symptoms, increase morbidity and prolonged intensive care unit stay	153
<i>Legionella pneumophila</i>	Pneumonia	154
<i>Enterobacter cloacae</i>	Pneumonia	155
<i>Acinetobacter baumannii</i>	Pneumonia	146,155
<i>Klebsiella pneumoniae</i>	Pneumonia	146
<i>Mycoplasma pneumoniae</i>	Interstitial pneumonia	149
<i>Mycoplasma pneumoniae</i>	Not reported	151
<i>Legionella pneumophila</i>	Not reported	151
<i>Streptococcus pneumoniae</i>	Not reported	151
<i>Prevotella</i>	Not reported	156–158
<i>Haemophilus</i>	Not reported	158,159
<i>Lautropia</i>	Not reported	159
<i>Cutibacterium</i>	Not reported	159

an infection in individuals with a weakened immune system. It has been noted that the SARS-CoV-2 infection can damage the cells and the lung infrastructure.<sup>160</sup> Subsequently, the changed condition enables bacteria to increase adherence and invasion (Figure 1). It has been found that the mortality rate of viral pandemics is heavily impacted by secondary bacterial infections with myriad numbers of people in the 1918 influenza pandemic as well as the 2009 pandemic, who died from secondary bacterial infections rather than the virus alone.<sup>26,27,161</sup>

Despite the proven significance of co-infections in the severity of respiratory diseases, these kinds of infections during large outbreaks of respiratory infections are under-determined.<sup>162</sup> For the precise diagnosis and evaluation of co-infections during the COVID-19 pandemic, samples must be taken longitudinally throughout the disease course via techniques independent of the culture for identifying mixed infections such as whole-genome metagenomics (WGMs).<sup>162</sup> Such works offer valuable monitoring findings on co-infection pathogens and drug-resistance infections resulting in improved antibiotic prescribing options.<sup>162</sup>

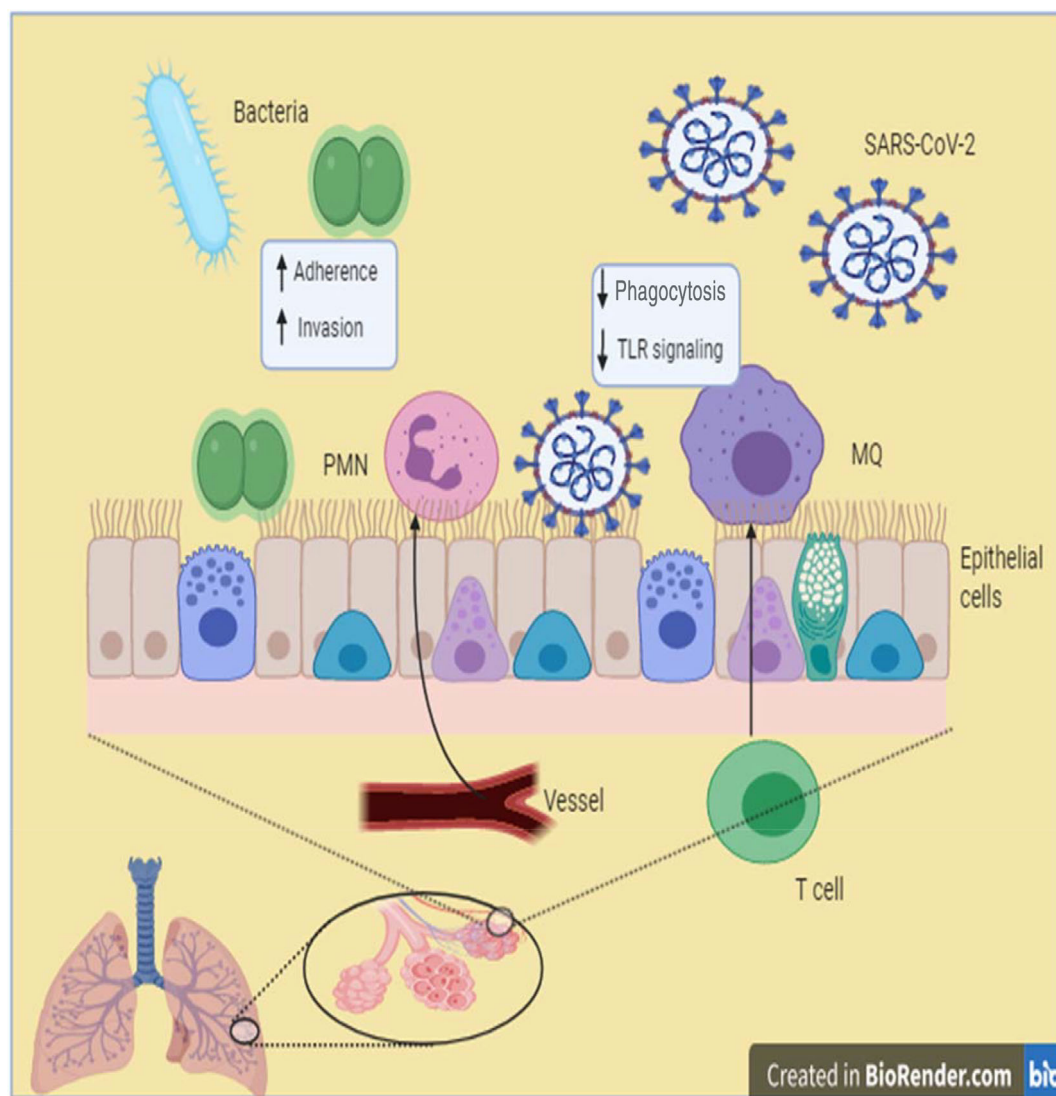
Zhou et al.<sup>163</sup> found that in the current COVID-19 pandemic, 50% of patients who died from Covid-19 had bacterial co-infections. Correspondingly, Chen et al.<sup>146</sup> have reported fungal and bacterial co-infections in patients with COVID-19. COVID-19 patients are hospitalized on invasive mechanical ventilation for a long time, leading to higher chances of using a ventilator and hospital-acquired infections.<sup>162</sup> Thus, the rapid diagnosis of a broad range of potential pathogens and antimicrobial resistances for subsequent monitoring of co-infection would be crucial. The metagenome of COVID-19 patients has shown that *Prevotella* is a key player in immune response in a Chinese study,<sup>156</sup> while other opportunistic pathogens were found in a study conducted in the USA.<sup>157–159,164</sup> There is a wide range of bacterial pathogens including *Haemophilus*, *Lautropia*, *Prevotella* have been detected as co-infection in Brazil, China, and the USA.<sup>157–159,164</sup>

However, a further concern with the rapid expansion of critical care capacity to manage SARS-CoV-2 can potentially increase the rate of nosocomial infection within the hospital environment.<sup>165</sup> To date, although the role of viral or bacterial co-infection in SARS-CoV-2 remains elusive, only a few SARS-CoV-2 patients worldwide have had documented evidence of co-infection; however, there is still a concern on this issue as many reports claim that a significant proportion of COVID-19 patients developed bacterial co-infections.

### 1.5 | The era of post-COVID-19 and antimicrobial resistance bacteria

It has been noted during the current pandemic, the antibiotic administration has been frequently used for COVID-19 patients who were admitted to the intensive care unit.<sup>165</sup> While scientists attempt to understand and control the COVID-19 pandemic, it would be also critical to prepare for the effect of the current and future viral pandemics on secondary bacterial infections, resulting in antimicrobial resistance in the near future. In combination with using an antimalarial drug, hydroxyl-chloroquine, azithromycin has become a popular therapeutic option for COVID-19 patients. Reports demonstrated that a combination of hydroxyl-chloroquine and azithromycin was effective for a large proportion of Covid-19 patients.<sup>166,167</sup> It is hard to estimate how often this combination is prescribed, but such a rate would be high enough to cause a shortage of azithromycin. However, 30–40% of common types of bacterial agents are already resistant to azithromycin, and overuse could render this or other antibiotics even less effective.<sup>168</sup> The findings could help experts' advice on using the antibiotics in COVID-19 patients and help them to better understand the spread of





**FIGURE 1** Postulated schematic of bacterial coinfection with SARS-CoV-2 infection. It has been proposed when SARS-CoV-2 infects lung cells can damage the cells and the lung infrastructure.<sup>160</sup> This situation attracts neutrophil and macrophages to the site of infection and promoting the inflammation.<sup>160</sup> Finally, the changed situation and epithelial damage can cause bacteria to adhere to and invasion of the cells and proliferation. MQ, macrophage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

co-infections in hospitals and the mechanism of bacterial-viral coinfection. One factor that involves in the antibiotic resistance in bacterial co-infection is the widespread use of antibiotics in COVID-19 patients. Emerging data show that more than 90% of COVID-19 patients receive antibacterial drugs.<sup>169,170</sup> This rapid increase in antibiotic administration can cause a strong selective pressure on bacterial pathogens to evolve resistance leading to the increased incidence of drug-resistant bacterial infections in the years subsequent to the COVID-19 pandemic. It was estimated that 10 million people could die from an antibiotic-resistant bacterial infection in the year of 2050,<sup>171</sup> but such prediction may be altered and shortened because of the devastating impact of the COVID-19 pandemic on the usage of antibiotics, so this timeline

will almost have to be modified. Nevertheless, concerted efforts must be made to better understand antibiotic administration in COVID-19 patients. Antibiotics do not directly act on viral infections but viral respiratory infections often lead to bacterial co-infections.<sup>30–32</sup> The current pandemic highlights the necessity for understanding the complex relationship between viral and bacterial infections. Of note, in patients who have treated with high-dose antibiotics may have more co-infections with drug-resistant bacteria.

Additionally, a recent clinical trial conducted by Hagan et al<sup>172</sup> demonstrated that the use of broad-spectrum antibiotics (which led to depleting gut microbiota) decreased and impaired the immune system's ability to generate antibodies. Also, the current study shows that the use of

**TABLE 4** Several functional suggestions for management and control of bacterial co-infection with COVID-19

Suggestion	Description
Using a broad-spectrum diagnostic panel	Improves diagnosis, evaluation, and clinical management of patients with other respiratory viral infection concurrent with COVID-19
Developing novel treatment and prevention strategies	Increases our knowledge about the underlying molecular mechanisms accounting for viral-bacterial co-infection to promote novel therapeutic and prevention approaches
Performing antibacterial susceptibility tests and potential therapy	Prevents reduced antimicrobial susceptibility and treatment failure due to co-infections <sup>174</sup>
Considering the biofilm-associated bacterial infections	Facilitates treatment management as biofilm formation on artificial devices has been observed previously, thereby affecting infection outcomes, especially in COVID-19 patients under mechanical ventilation <sup>175</sup>
Classifying mechanisms of pathogen interactions	Increases the ability of infection control as the extension of chemotherapy-resistant pathogens is a severe global obstacle <sup>174</sup>

antibiotics perturbed bile acid metabolism and induced inflammatory responses.<sup>173</sup> Hence, improved functional therapies, including antibiotics and alternative therapies as well as the prediction of bacterial respiratory infections using vaccines, should be regarded as potential therapeutic approaches. Besides, standard guidelines should also be established for the administration of the antibiotics. In addition to the direct effect on drug-resistant bacteria as a result of enhanced antibiotic administration, the transmission of drug-resistant bacteria through the medical system should be taken into account. The COVID-19 pandemic has highlighted the importance of vaccination, the need for functional antimicrobials, as well as the necessity for supporting research into the understanding and control of co-infections. Rapid characterization of co-infection is essential in the treatment of the most COVID-19 patients, and could help to save lives, and will improve antimicrobial stewardship during the pandemic. Additionally, mixed bacterial-viral infections can result in antibiotic treatment

failure. These observations show that a better understanding of the underlying mechanisms will enable researchers to design effective preventive and therapeutic options. Several functional suggestions for management and control of bacterial co-infection with COVID-19 are offered in Table 4.



## 2 | CONCLUSION

Respiratory viruses such as SARS-CoV-2 are well-characterized to cause severe disorders and pneumonia, particularly in individuals with serious medical comorbidities and aged populations. Additionally, respiratory virus infection could usually lead to enhanced susceptibility to secondary bacterial infections. However, the mechanisms responsible for bacterial-SARS-CoV-2 co-infection require further study. It has been noted that an elicited adaptive immune reaction toward viral infection fails the reaction of the host innate immunity against bacterial infection. This situation can explain why bacterial co-infections occur when the virus starts to be eradicated from the lungs of patients with COVID-19. This is accompanied by a shift in phagocytic activity of lung cells that mediate basal levels of innate protection via phagocytosis and pro-inflammatory cytokines formation to cells better attuned to antigen presentation and stimulation of adaptive immune reactions. Additionally, recently it has been found the microbiome diversity shapes our immune system. In line with this, the depletion of the gut microbiome hinders the immune system's ability to create a humoral response against viruses like the flu virus. However, this novel paradigm ultimately allows the development of new immune intervention approaches for the prevention and management of viral-bacterial co-infections in COVID-19 patients. The COVID-19 pandemic reinforces the importance of preventative measures such as vaccination and antimicrobial treatments in maintaining human health.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## ORCID

Rasoul Mirzaei  <https://orcid.org/0000-0002-4148-6495>  
Sajad Karampoor  <https://orcid.org/0000-0003-3716-8096>

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